

Intima-Media Thickening of the Radial Artery After Transradial Intervention

An Intravascular Ultrasound Study

Takatoshi Wakeyama, MD, Hiroshi Ogawa, MD, Hiroshi Iida, MD, Akira Takaki, MD, Takahiro Iwami, MD, Mamoru Mochizuki, MD, Takeo Tanaka, MD

Yamaguchi, Japan

OBJECTIVES	We sought to assess the extent and nature of radial artery injury after transradial intervention (TRI) using intravascular ultrasound (IVUS).
BACKGROUND	Although TRI has been developed to minimize bleeding and improve the quality of life, radial artery injury is a problem.
METHODS	We studied 100 radial arteries in 100 consecutive patients who underwent coronary IVUS imaging. To assess the injury to the radial artery, we compared the radial artery findings between first-TRI patients ($n = 48$) and repeat-TRI patients ($n = 52$). Ten cross-sections at 5-mm intervals from the puncture site along a 50-mm distance were measured in each patient.
RESULTS	In repeat-TRI patients, the lumen area (LA) and minimal lumen diameter (MLD) were smaller than those in first-TRI patients ($p = 0.032$ and $p = 0.028$, respectively), whereas the intima-media cross-sectional area (IMCsa) and intima-media thickness (IMT) were significantly greater than those in first-TRI patients ($p < 0.01$). In the proximal radial artery, there were no significant differences in the vessel area (VA), LA, IMCsa, or MLD between the two groups. In the distal radial artery, both LA and MLD were significantly smaller in repeat-TRI patients than in first-TRI patients ($p < 0.01$), whereas IMCsa and IMT were greater in repeat-TRI patients than in first-TRI patients ($p < 0.01$). However, VA did not differ between the two groups.
CONCLUSIONS	The lumen diameters were smaller in repeat-TRI patients than in first-TRI patients due to intima-media thickening, especially in the distal radial artery. Care should be taken when the radial artery is used as a conduit in coronary artery bypass graft surgery, particularly in patients who have undergone TRI. (J Am Coll Cardiol 2003;41:1109–14) © 2003 by the American College of Cardiology Foundation

There are few reports on radial artery injuries after using the transradial approach (1,2). Patients with ischemic heart disease usually undergo repeated coronary angiographic studies because of restenosis after percutaneous coronary intervention (PCI). Therefore, it is desirable for the radial artery to be patent as an access for coronary angiography and PCI. On the other hand, the radial artery has been established the second positions, which follow the left internal thoracic artery (LITA) in coronary artery bypass graft surgery (CABG) (3). It is anticipated that injury to the radial artery will become a problem, not at first, but at a later date. Recently, we have shown that the inner diameter of the radial artery decreases after transradial intervention (TRI), and flow velocity of the ulnar artery increases as a compensatory mechanism (4). It is not known whether the narrowing of the radial artery is due to intimal hyperplasia or to vascular shrinkage. In this study, we examined the narrowing of the radial artery and the extent of injury using intravascular ultrasound (IVUS).

METHODS

Study patients. From November 2000 to March 2002, we studied 100 consecutive patients who underwent coronary IVUS imaging, which was used to examine the radial artery after the coronary procedures. The patients' clinical characteristics and catheterization procedures are summarized in Table 1. Oral witnessed informed consent was obtained from all patients before the study.

Procedural protocol and IVUS imaging systems. A TRI was performed with 6F-long sheath (16 cm; Terumo Co., Tokyo, Japan) in all patients at our institute. After coronary IVUS imaging, a guide wire (0.014 in.) was inserted from the sheath into the brachial artery, passing through the radial artery. After the sheath was extracted through the puncture site, an imaging catheter was introduced along the 0.014-in. guide wire, and IVUS of the radial artery was performed. Intra-radial isosorbide dinitrate (1.0 mg) was administered just before IVUS imaging. The IVUS examinations were performed with a 40-MHz, 3.5F transducer (CIVIS, Boston Scientific) and a dedicated imaging console. In all studies, the transducer was withdrawn at 1.0 mm/s, within the stationary imaging sheath, using a motorized pullback device. Automatic pullbacks were per-

From the Division of Cardiology, Tokuyama Central Hospital, Tokuyama, Yamaguchi, Japan.

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Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
IMcsa	= intima-media cross-sectional area
IMT	= intima-media thickness
IVUS	= intravascular ultrasound
LA	= lumen area
LITA	= left internal thoracic artery
MLD	= minimal lumen diameter
PCI	= percutaneous coronary intervention
TRI	= transradial intervention
VA	= vessel area

formed up to the sheath, and the ultrasound images were recorded onto 0.5-in. super-VHS videotapes for off-line analysis.

Quantitative IVUS measurement. The IVUS images were digitized, and a quantitative analysis was performed with custom-developed software for geometric computations (National Institutes of Health [NIH] Image). Quantitative analyses consisted of measurements of the lumen area (LA) and the vessel area (VA) (Fig. 1). The VA was defined as the border between the hypoechoic media zone and the surrounding echo-bright adventitia. The intima-media cross-sectional area (IMcsa) was calculated as the difference between the VA and the LA. The measurements were taken from 50 mm proximal to the puncture site. Then, 10 cross sections at 5-mm intervals were measured along the 50-mm distance for each patient. A mean value of the 10 cross sections was calculated, and the segments for IVUS measurements were defined as follows: the distal radial artery extended from the puncture site to the 25-mm

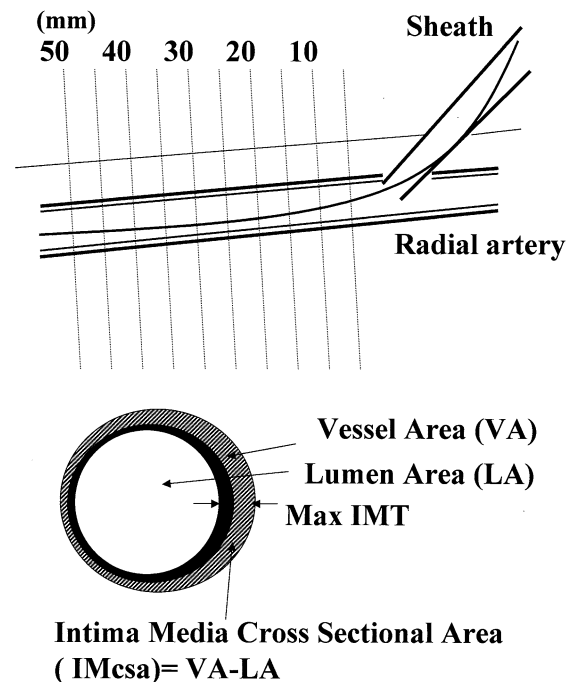


Figure 1. (Top) Schematic representation of intravascular ultrasound (IVUS) analysis of the radial artery. Ten cross sections at 5-mm intervals were measured along 50 mm. (Bottom) Schematic representation of IVUS analysis of a radial artery cross-sectional image. IMcsa = intima-media cross-sectional area; IMT = intima-media thickness.

point, and the proximal radial artery extended from that 25-mm point to the 50-mm point distal to the puncture site.

Statistical analysis. Statistical analysis was performed using StatView version 5.0. Quantitative data are expressed as the mean value \pm SD, and qualitative data are presented as frequencies. Continuous variables were compared using the *t* test, and categorical variables were compared using the Fisher exact test. Because there are traditional risk factors known to be associated with intima-media thickness (IMT) (5,6), the influence of these factors on the association between repeated TRI and intima-media thickening was examined by multiple linear regression analysis. Of the independent variables, both age and body mass index (kg/m^2) were treated as continuous variables. Other independent variables were treated as categorical variables, which were coded as the following dummy variables: cigarette smoking (20 cigarettes/day for >10 years; 0 for nonsmokers and 1 for smokers); repeated TRI (history of more than 1 TRI; 0 for first TRI and 1 for repeated TRI); hypertension (blood pressure $\geq 140/90$ mm Hg or current antihypertensive medication; 0 for normotension and 1 for hypertension); diabetes mellitus (according to the World Health Organization criteria or current antidiabetic medication; 0 for absence and 1 for presence); and hyperlipidemia (serum cholesterol ≥ 220 mg/dl; 0 for absence and 1 for presence). A *p* value <0.05 was considered statistically significant.

Table 1. Clinical Characteristics of Study Patients

	Repeat-TRI Group (n = 52)	First-TRI Group (n = 48)	p Value
Age (yrs)	67 \pm 7	66 \pm 8	0.31
Gender (male/female)	47/5	38/10	0.16
Risk factors			
Diabetes	10 (19%)	9 (19%)	>0.99
Hypertension	36 (69%)	32 (67%)	0.83
Hyperlipidemia	30 (58%)	26 (54%)	0.38
Smoking	9 (17%)	18 (37%)	0.026
Vessel disease			
1 vessel	21 (40%)	25 (52%)	0.31
2 vessel	28 (54%)	20 (42%)	0.23
3 vessel	3 (6%)	3 (6%)	>0.99
Approach			
Right radial artery	48 (92%)	40 (83%)	0.22
Left radial artery	4 (8%)	8 (17%)	0.22
History of TRI			
First	0	48	
Second	41	0	
Third	7	0	
Fourth	4	0	
History of radial artery spasm	5 (10%)	0	

Data are presented as the mean value \pm SD or number (%) of patients.
TRI = transradial intervention.

Table 2. Quantitative Intravascular Ultrasound Data

	Repeat-TRI Group (n = 52)	First-TRI Group (n = 48)	p Value
Radial artery (average 5–50 mm)			
LA (mm ²)	5.05 ± 1.26	5.62 ± 1.35	0.032
VA (mm ²)	7.72 ± 1.64	7.85 ± 1.79	0.710
IMcsa (mm ²)	2.67 ± 0.59	2.22 ± 0.67	0.0007
IMT (mm)	0.40 ± 0.08	0.30 ± 0.07	< 0.0001
MLD (mm)	2.37 ± 0.31	2.51 ± 0.33	0.028
Distal radial artery (5–25 mm)			
LA (mm ²)	4.50 ± 0.99	5.27 ± 1.21	0.0008
VA (mm ²)	7.39 ± 1.40	7.52 ± 1.62	0.674
IMcsa (mm ²)	2.89 ± 0.68	2.24 ± 0.65	< 0.0001
IMT (mm)	0.46 ± 0.10	0.31 ± 0.07	< 0.0001
MLD (mm)	2.23 ± 0.26	2.43 ± 0.32	0.0015
Proximal radial artery (30–50 mm)			
LA (mm ²)	5.59 ± 1.80	5.96 ± 1.71	0.303
VA (mm ²)	8.04 ± 2.12	8.17 ± 2.16	0.764
IMcsa (mm ²)	2.44 ± 0.56	2.20 ± 0.69	0.059
IMT (mm)	0.34 ± 0.08	0.28 ± 0.07	0.0004
MLD (mm)	2.49 ± 0.42	2.58 ± 0.39	0.256

Data are presented as the mean value ± SD.

IMcsa = intima-media cross-sectional area; IMT = intima-media thickness; LA = lumen area; MLD = minimal lumen diameter; TRI = transradial intervention; VA = vessel area.

RESULTS

Baseline characteristics. The baseline characteristics of the subjects are summarized in Table 1. There were no differences in the clinical characteristics, except for smoking, between repeat-TRI and first-TRI patients. Repeat-TRI patients included 41 patients with 2 TRIs, seven with 3 TRIs, and four with 4 TRIs, as well as five patients who had significant spasm during a previous TRI.

Comparison of IVUS measurements. Table 2 shows the IVUS parameters in first-TRI and repeat-TRI patients. There was no difference in VA between the two groups, but LA and the minimal lumen diameter (MLD) were smaller in repeat-TRI patients than in first-TRI patients. In addition, IMcsa and IMT were significantly greater in repeat-TRI patients than in first-TRI patients. In the proximal radial artery, there were no significant differences in VA, LA, IMcsa, or MLD between the two groups, but IMT was greater in repeat-TRI patients than in first-TRI patients. In the distal radial artery, LA and MLD were significantly smaller in repeat-TRI patients than in first-TRI patients, whereas IMcsa and IMT were greater in repeat-TRI patients than in first-TRI patients. However, VA did not differ between the two groups. Quantitative measurements of the 10 cross sections are shown in Tables 3 and 4. The LA was significantly smaller in the segment 10 to 25 mm from the puncture site in arteries subjected to repeat-TRI than in the respective segments in first-TRI arteries. However, there was no difference in LA values measured in the segment 30 to 50 mm from the puncture site between the two groups. On the other hand, there were no significant differences in VA in any segment. The IMcsa was significantly larger in the segment 5 to 30 mm from the puncture site in repeat-TRI patients than in respective segments in first-TRI patients, but in the segments 35 to 50 mm from

the puncture site, the difference did not achieve statistical significance. Table 4 shows MLD and IMT in the 10 cross sections. The MLD was smaller in the segments from 10 to 25 mm in repeat-TRI patients than in the respective segments in first-TRI patients. The IMT in repeat-TRI patients was increased in all segments, except for the segment 40 mm from the puncture site. Figure 2 shows two cases that have undergone repeated TRI, and the IMcsa at 10 to 20 mm from the puncture site was significantly greater than the segment at 40 mm. In the case of patient S.T., the segment from 10 to 20 mm had a plaque-like appearance.

Multiple regression analysis of IMT (Table 5). Multivariate analysis of the associations was performed using standard linear regression techniques, using the IMT of the radial artery as the dependent variable. A history of TRI and traditional risk factors, including hypertension, diabetes mellitus, smoking, hyperlipidemia, age, and body mass index, were included as co-variables in the multivariate analysis. Repeated TRI and age were independently associated with IMT, as shown in Table 5. Repeated TRI was the most powerful independent predictor of the increase in IMT of the radial artery.

DISCUSSION

Intima-media thickening of radial artery after TRI.

Although TRI has been shown to be a safe alternative to the transfemoral approach (7,8), there has been some concern about possible complications, especially regarding the occurrence of radial artery occlusion in the early phase, and intima-media thickening of the radial artery in the long term. Key factors in the prevention of radial artery occlusion might be anticoagulation (9), immediate post-procedural sheath removal (1,10,11), and a small sheath/radial artery ratio (1,9,10). Although it would be possible to prevent the

Table 3. Quantitative Intravascular Ultrasound Data

	Distance From the Puncture Site	Repeat-TRI Group (n = 52)	First-TRI Group (n = 48)	p Value
LA (mm ²)	5 mm	4.20 ± 1.27	4.46 ± 2.78	0.388
	10 mm	4.28 ± 1.11	5.06 ± 2.16	0.004
	15 mm	4.40 ± 1.28	5.30 ± 1.59	0.003
	20 mm	4.81 ± 1.53	5.80 ± 1.82	0.005
	25 mm	4.84 ± 1.50	5.76 ± 1.75	0.007
	30 mm	5.11 ± 1.61	5.55 ± 1.63	0.199
	35 mm	5.54 ± 2.09	5.95 ± 2.05	0.335
	40 mm	5.89 ± 2.11	5.90 ± 2.10	0.984
	45 mm	5.74 ± 2.02	6.12 ± 2.01	0.363
	50 mm	5.83 ± 2.35	6.30 ± 2.41	0.348
VA (mm ²)	5 mm	7.21 ± 1.77	6.72 ± 1.92	0.202
	10 mm	7.25 ± 1.62	7.28 ± 1.85	0.931
	15 mm	7.30 ± 1.60	7.57 ± 1.99	0.456
	20 mm	7.57 ± 1.84	8.06 ± 2.18	0.248
	25 mm	7.55 ± 1.81	7.97 ± 2.14	0.313
	30 mm	7.74 ± 1.88	7.76 ± 2.08	0.969
	35 mm	8.04 ± 2.47	8.21 ± 2.52	0.745
	40 mm	8.31 ± 2.43	8.10 ± 2.50	0.688
	45 mm	8.09 ± 2.41	8.26 ± 2.40	0.731
	50 mm	8.17 ± 2.61	8.51 ± 2.85	0.546
IMcsa (VA – LA; mm ²)	5 mm	3.01 ± 0.86	2.26 ± 0.71	< 0.0001
	10 mm	2.97 ± 0.84	2.22 ± 0.72	< 0.0001
	15 mm	2.89 ± 0.71	2.27 ± 0.68	< 0.0001
	20 mm	2.76 ± 0.68	2.25 ± 0.67	0.0004
	25 mm	2.71 ± 0.77	2.20 ± 0.67	0.0008
	30 mm	2.62 ± 0.73	2.20 ± 0.68	0.005
	35 mm	2.50 ± 0.67	2.25 ± 0.75	0.097
	40 mm	2.41 ± 0.60	2.20 ± 0.72	0.122
	45 mm	2.34 ± 0.60	2.14 ± 0.71	0.124
	50 mm	2.34 ± 0.53	2.22 ± 0.77	0.376

Data are presented as the mean value ± SD.
Abbreviations as in Table 2.

incidence of radial artery occlusion after TRI in this way, intima-media thickening of the radial artery is a more important problem because the artery is a necessary conduit for CABG. The diameter of the radial artery gradually decreases peripherally (Table 4), and among Japanese adult patients with ischemic heart disease, the inner diameter of the radial artery at the puncture site was 2.43 mm, on average, in this study. This result is in line with that of previous studies obtained by transcatheter ultrasound (2,4,12). However, the outer diameter of the 6F-long sheath (16 cm; Terumo Co.) is 2.52 mm. In this study population, the mean inner diameter of the radial artery was smaller than 2.52 mm in the distal segment (Table 4). Thus, the distal radial artery was expanded by the sheath insertion, like in balloon angioplasty. The extensive structural damage caused by sheath insertion may be the primary trigger for the events that lead to intimal hyperplasia and vascular remodeling (13,14). The greater IMT of the distal radial artery observed in repeat-TRI patients in this study indicates that the radial artery is indeed injured during insertion of the sheath. In contrast, there were no differences in the IMT or IMcsa of the proximal radial artery between repeat-TRI and first-TRI patients, probably due to the fact

Table 4. Quantitative Intravascular Ultrasound Data

	Distance From the Puncture Site	Repeat-TRI Group (n = 52)	First-TRI Group (n = 48)	p Value
MLD (mm)	5 mm	2.15 ± 0.39	2.21 ± 0.46	0.501
	10 mm	2.17 ± 0.30	2.37 ± 0.38	0.005
	15 mm	2.19 ± 0.37	2.43 ± 0.41	0.004
	20 mm	2.34 ± 0.42	2.56 ± 0.46	0.014
	25 mm	2.34 ± 0.38	2.57 ± 0.44	0.008
	30 mm	2.38 ± 0.40	2.48 ± 0.41	0.248
	35 mm	2.46 ± 0.51	2.56 ± 0.49	0.328
	40 mm	2.57 ± 0.48	2.57 ± 0.45	0.952
	45 mm	2.55 ± 0.45	2.63 ± 0.45	0.351
	50 mm	2.55 ± 0.52	2.67 ± 0.52	0.265
Maximal IMT (mm)	5 mm	0.49 ± 0.11	0.32 ± 0.09	< 0.0001
	10 mm	0.48 ± 0.13	0.31 ± 0.09	< 0.0001
	15 mm	0.46 ± 0.14	0.31 ± 0.08	< 0.0001
	20 mm	0.43 ± 0.12	0.30 ± 0.07	< 0.0001
	25 mm	0.42 ± 0.15	0.31 ± 0.09	< 0.0001
	30 mm	0.38 ± 0.13	0.29 ± 0.07	0.0002
	35 mm	0.36 ± 0.10	0.29 ± 0.09	0.001
	40 mm	0.33 ± 0.09	0.29 ± 0.11	0.054
	45 mm	0.32 ± 0.09	0.27 ± 0.08	0.007
	50 mm	0.32 ± 0.08	0.28 ± 0.08	0.032

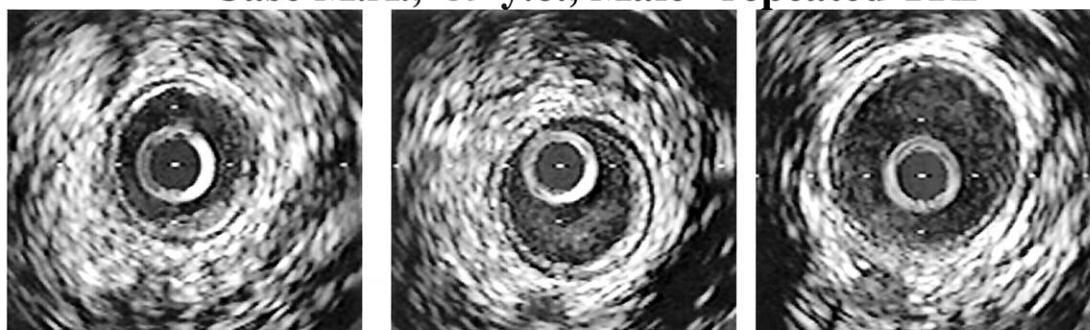
Data are presented as the mean value ± SD.
Abbreviations as in Table 2.

that the mean diameter of the proximal radial artery was >2.52 mm (Table 4). These results indicate that injury to the distal radial artery was more severe than that to the proximal radial artery.

In clinical coronary restenosis after balloon angioplasty, negative remodeling is as important as intimal hyperplasia (14). There were no differences in the VA of the distal and proximal radial artery between the two groups in this study. This finding shows that narrowing of the distal radial artery plays a more dominant role in intimal hyperplasia than negative remodeling. The major difference between clinical coronary restenosis and an increase in IMT of the radial artery after TRI is the severity of injury. In clinical coronary angioplasty, the injury to both the media and adventitia results in cell proliferation and collagen synthesis, thus expanding the adventitia. Subsequent maturation of collagen is associated with contraction and overall vessel shrinkage (15). On the other hand, the increase in IMT of the radial artery after TRI is similar to the gentle denudation injury induced in animal models. Because it is considered that sheath insertion into the radial artery promotes injury to the intima or media but does not promote deep arterial injury, intima-media thickening appeared to be more crucial than negative remodeling in terms of the narrowing of the radial artery after TRI in this study.

Length of injured radial artery and CABG. The radial artery is considered as devoid of atherosclerosis and is commonly used as a conduit in CABG. A recent histologic study has shown that intimal hyperplasia is consistent with early atherosclerosis in the radial artery and the radial artery is more likely to present atherosclerosis than LITA (6,16).

Case M.A., 59 y.o., Male repeated TRI

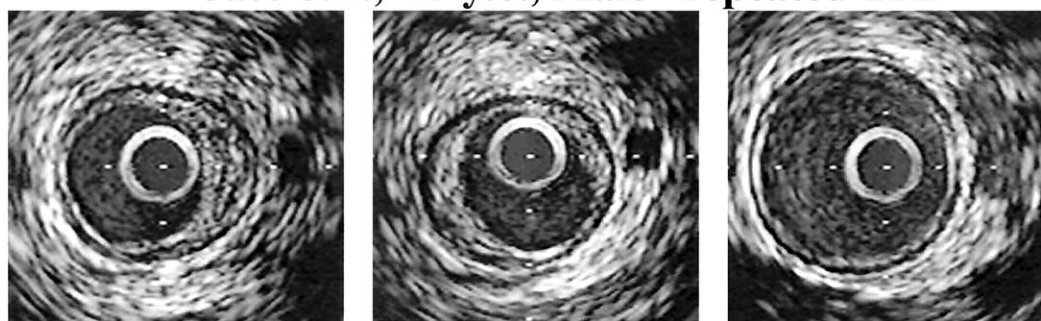


10mm

20mm

40mm

Case S.T., 73 y.o., Male repeated TRI



10mm

20mm

40mm

Figure 2. Case M.A. is a 59-year-old man. The intima-media thickness at 10 to 20 mm from the puncture site was significantly greater than that at the 40-mm segment. Case S.T. is a 73-year-old man. The 10- to 20-mm segment had a plaque-like appearance. TRI = transradial intervention.

This study showed that injury to the distal radial artery was more severe than that to the proximal radial artery. Moreover, radial arteries were observed in detail, and injuries were prominent at 3 cm from the puncture site, and slightly beyond 3 cm. This intima-media thickening of the radial artery does not usually become a problem for subclinical applications, but it is known to become a problem when CABG is required in the future.

Future strategy of TRI. As discussed earlier, the major etiology of intima-media thickening in the radial artery is the use of a sheath larger than the radial artery. Although we used a 6F sheath for TRI in this study, TRI using a 5F

system has recently become available. Because the outer diameter of the 5F sheath is 2.19 mm (Terumo Co.) and the MLD of first TRI is 2.19 mm or more (Table 4), vascular injury will be less than with the 6F sheath. In addition, it is also believed that local drug elution from the sheath to the radial artery may also be effective.

Conclusions. In the repeat-TRI patients, the lumen diameter was smaller than that in the first-TRI patients due to intima-media thickening, especially in the distal radial artery. Care should be taken when the radial artery is used as a conduit in CABG, particularly in patients who have undergone TRI.

Table 5. Multiple Regression Analysis of Intima-Media Thickness

	Regression Coefficient	Standard Error	Standard Regression Coefficient	T Value	95% CI	p Value
TRI	0.097	0.015	0.551	6.367	0.067–0.127	< 0.0001
Age	0.003	0.001	0.262	2.797	0.001–0.005	0.0064
Hyperlipidemia	−0.02	0.016	−0.114	−1.273	−0.052–0.011	0.206
Hypertension	0.016	0.016	0.082	0.972	−0.016–0.047	0.334
BMI	0.002	0.003	0.051	0.547	−0.004–0.008	0.585
Diabetes	0.009	0.018	0.041	0.474	−0.028–0.045	0.637
Smoking	0.001	0.018	0.005	0.051	−0.034–0.036	0.959
Constant	0.069	0.120	0.069	0.571	−0.171–0.308	0.569

BMI = body mass index; CI = confidence interval; TRI = transradial intervention.

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Reprint requests and correspondence: Dr. Takatoshi Wakeyama, Division of Cardiology, Tokuyama Central Hospital, 1-1 Kodachou, Tokuyama, Yamaguchi, 745-8522 Japan. E-mail: wakeyama@hotmail.com.

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